CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207103Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	January 15, 2015
Reviewer(s):	Mona Patel, Pharm.D. Division of Risk Management
Acting Team Leader:	Naomi Redd, Pharm.D. Division of Risk Management
Acting Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Subject:	Review to determine if a REMS is necessary
Drug Name(s):	Ibrance (palbociclib)
Therapeutic Class:	Cyclin Dependent Kinase 4/6 Inhibitor
Dosage and Route:	125 mg orally once daily for 21 days followed by 7 days off in combination with letrozole 2.5 mg orally once daily given continuously
Division:	Division of Oncology Products – 1 (DOP-1)
Application Type/Number:	NDA 207103
Applicant/sponsor:	Pfizer Inc.
OSE RCM #:	2014-1273 2014-1282

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) Ibrance (palbociclib). The applicant, Pfizer Inc., submitted a New Drug Application (NDA) 207103 for palbociclib for use in combination with letrozole for the treatment of postmenopausal, ER-positive, HER2-negative advanced breast cancer who have not received previous systemic treatment.

Pfizer submitted a risk management plan with identified risks of myelosuppression and potential risks of QT prolongation, interstitial lung disorder/pneumonitis, cataract/lens degeneration, hyperglycemia, and decreased spermatogenesis. In this pharmacovigilance plan, the Sponsor proposes to manage these events through routine pharmacovigilance and product labeling. The Sponsor did not submit a REMS.

1.1 BACKGROUND

Breast cancer is the second leading cause of cancer death in women, with nearly 40,000 deaths per year. The American Cancer Society estimates that approximately 232, 670 new cases of invasive breast cancer will be diagnosed in women in 2014. [1] Breast cancer tumor types are distinguished by hormonal receptor status, with approximately 80% of breast cancer cases in women being ER-positive tumors in women aged 45 years and older (the median age of breast cancer diagnosis in women is 61).[2,3] The current first-line treatment in the ER-positive, HER2-negative advanced breast cancer postmenopausal population includes endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen. Despite the availability of these medications, the prognoses in advanced breast cancer patients remain poor. Patients will eventually develop resistance to these medications, resulting in progression of disease. In the metastatic disease setting, targeted antihormonal therapies including letrozole prolong the time to progression/progression free survival from 5 to 15 months.[4] There are no approved products used in combination with letrozole in the first-line advanced breast cancer setting in current standard of care guidelines, thus, there is a clear need to address this serious condition with new therapies in order to increase overall survival and ameliorate the symptoms of breast cancer.

Palbociclib – Palbociclib is a first in class oral, reversible inhibitor of cyclin dependent kinase (CDK) 4/cyclin D1 kinase as well as CDK 6/cyclin D1 kinase. During cell proliferation, the G1 to S transition of the cell cycle is under the control of CDKs which are activated through specific formation with regulatory cyclins. CDK 4 and CDK 6 are activated by binding to D-type cyclins in early G1 phase. This dual inhibition prevents

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[1] http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics accessed 11/28/14.

[2] Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999; 17(5): 1474-81.

[3] Draft clinical review by Drs. Julia Beaver & Laleh Kordestani (v. December 29, 2014)

[4] Palbociclib Summary of Clinical Efficacy Section 2.7.3

cellular DNA synthesis and thus inhibits cell division.[5] Preclinical data also indicated that palbociclib may be expected to cause both growth arrest as well as secondary cytoreductive effect.[4] The proposed indication for palbociclib is for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received prior systemic treatment for their advanced disease. The recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food in combination with letrozole 2.5 mg once daily given continuously. (b) (4)

1.2 REGULATORY HISTORY

The review timeline for this application is Priority, and is undergoing accelerated approval. Listed below are the pertinent regulatory history milestones for this NDA:

- March 9, 2004 – IND 69324 submitted for palbociclib
- April 9, 2013 – Breakthrough Therapy Granted
- June 30, 2014 – Part 1 of Rolling NDA application received
- August 13, 2014 – Part 2 of Rolling NDA application received
- November 13, 2014 – Midcycle meeting
- December 4, 2014 – Midcycle teleconference with the sponsor
- PDUFA (Action) date – April 13, 2015

2 MATERIALS REVIEWED

- Pfizer Clinical Modules (sections 2.5, 2.7.3)
- Ibrance (palbociclib) draft label, December 16, 2014
- Draft clinical review by Drs. Julia Beaver & Laleh Kordestani (v. 12.29.14)

3 RESULTS OF REVIEW

Data from 18 studies were submitted to the NDA. This included the pivotal Phase 1/2 study (PALOMA1/A5481003), the confirmatory Phase 3 study (PALOMA2/A5481008), and two other clinical studies (A5481023, A5481004). Additional studies submitted included two bioavailability (BA) studies (A5481015, A5481021), four comparative BA and bioequivalence (BE) studies (A5481009, A5481020, A5481022, A5481036), three PK and tolerability studies (A5481011, A5481001, A5481010), four extrinsic factor PK studies (A5481012, A5481017, A5481018, A5481026) and a patient PD and PK/PD study (A5481002).

For the purpose of this NDA, the key clinical study is the Phase 2 portion of PALOMA1, Study A5481003 (noted as Study 1 in the substantially complete palbociclib label).[3]

[5] Clinical Overview (section 2.5), palbociclib

[6] Ibrance (palbociclib) draft label, January 14, 2015

3.1 OVERVIEW OF CLINICAL PROGRAM

At the time of this writing, FDA clinical reviewers were still completing analysis of the safety and efficacy of the studies outlined below. The summary below provides a high level overview of the studies that support this application.

Key Efficacy Findings: Please refer to the clinical review by Drs. Julia Beaver and Laleh Amiri Kordestani for the full review on efficacy and safety. The following is a summary of the key findings from substantially complete labeling for palbociclib as of January 14, 2015.

Study A5481003(Study-1)This was an open-label, randomized, Phase 1/2 trial to assess the efficacy, safety and pharmacokinetics of palbociclib plus letrozole and of letrozole alone for the first line treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

Patients enrolled in this study had a median age of 62.5 years in the palbociclib plus letrozole arm and 64 years in the letrozole alone arm. The majority of patients were Caucasian (89.7%) and all patients had an ECOG PS of 0 or 1. Forty nine percent of patients had de novo metastatic disease, 43% had received prior chemotherapy and 33% had received prior antihormonal therapy. (b) (4) percent of patients had bone only disease.[5]

The Phase 1 portion of the study was designed to confirm the safety and tolerability of the combination of palbociclib with letrozole and to exclude the potential of a drug-drug interaction with palbociclib and letrozole. Twelve patients were treated to establish the recommended phase 2 dose.

The phase 2 portion of the study was the basis of the application and was divided into two parts. One hundred sixty-five patients were randomized in Study 1. Part 1 included 66 biomarker-unselected patients randomized to receive palbociclib + letrozole or letrozole alone in a 1:1 fashion. Part 2 included 99 biomarker-positive (CCND1 gene amplification and/or loss of p16) patients randomized in the same fashion as in Part 1. Enrollment occurred in more than 10 countries worldwide.

The dosing and administration plan was as follows:

- Arm A (experimental arm): Palbociclib 125 mg/day orally for 3 weeks followed by 1 week off + letrozole 2.5 mg/day orally given continuously
- Arm B (control arm): letrozole 2.5 mg/day orally

Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.

The primary endpoint of the Phase 2 study was progression free survival (PFS) in the combined (Part 1 and Part 2) population. At the time of final analysis of PFS, overall survival (OS) events had been reported for 37% of patients. Median PFS was reported in favor of palbociclib plus letrozole of 20.2 months versus 10.2 months in the letrozole alone arm.[6]

3.2 SAFETY CONCERNS[6]

The safety of palbociclib (125 mg/day) plus letrozole (2.5 mg/day) versus letrozole alone was evaluated in a randomized, controlled trial (Study 1). The data described below reflect exposure to palbociclib in 83 out of 160 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of treatment in the randomized trial. The median duration of treatment for palbociclib was 13.8 months while the median duration of treatment on the letrozole-alone arm was 7.6 months.

The common treatment emergent adverse events (TEAEs) reported in ≥ (b) (4)% of patients in the palbociclib plus letrozole arm were neutropenia (74.7%), leukopenia (43.4%), fatigue (41.0%), anemia (34.9%), nausea (b) (4), (b) (4) alopecia (21.7%), and diarrhea (20.5%); while the most frequently reported TEAE in the letrozole alone arm was fatigue (23.4%).

Dose reductions due to an adverse reaction of any grade occurred in (b) (4)% of patients receiving palbociclib plus letrozole. The adverse events seen were generally managed by dose interruptions, cycle delays, dose reduction, and/or standard medical therapy. For adverse reactions requiring dose reduction, the dose was reduced to 100 mg/day with a second dose reduction to 75 mg/day if warranted. If further dose reduction below 75 mg/day was required, treatment was to be discontinued. For hematologic toxicities of Grade 3 ANC (<1000 to 500/mm^3) + Fever ≥38.5ºC and/or infection or Grade 4, palbociclib should be withheld until recovery to Grade ≤ 2, then resume at next lower dose. For Grade 3 non-hematologic toxicity (if persisting despite medical treatment), palbociclib should be withheld until symptoms resolve to Grade ≤ 1 or Grade ≤ 2 (if not considered a safety risk for the patient), and then resume at next reduced dose level.

Permanent discontinuation due to an adverse reaction occurred in (b) (4) of 83 ((b) (4)%) patients receiving palbociclib plus letrozole, and in 2 of 77 (2.6%) patients receiving letrozole alone. Neutropenia had the most permanent discontinuations but became less of an issue as investigators learned to manage.[3] No cases of febrile neutropenia, sepsis, or infection were reported in Phase 2 portion of the Study.

The adverse events of concern were Grade 3 or 4 neutropenia (62%), Grade 3 or 4 infections (5%), and pulmonary embolism (5%). These adverse events will be managed in labeling under separate subsections under Warnings and Precautions. (b) (4) embryo-fetal toxicity was a concern based on nonclinical safety findings and will also be addressed in the Warnings and Precautions section of the labeling.

Deaths: There were no deaths on-study in the Phase 1 part of PALOMA1. As of November 29, 2013, 1 of 83 patients in the palbociclib plus letrozole arm and 0 of the 77 patients in the letrozole alone arm died on-study (within 28 days of the last dose) in the Phase 2 part of PALOMA1. Per investigator assessment this one death was considered due to disease progression.[3]

Clinical Assessment Based on Pharmacology/Toxicology Findings[6]

(b) (4)

[redacted] As a variety of eye problems were seen in this open label study and the numbers were too small, no conclusions could be made.[3]

Embryo-fetal toxicity: Palbociclib is labeled as [redacted]. Based on the mechanism of action, palbociclib can cause fetal harm. Furthermore, palbociclib caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were greater than or equal to [redacted] times the human clinical exposure based on area under the curve (AUC). Females of reproductive potential are to use effective contraception during therapy with palbociclib and for at least 2 weeks after the last dose. Male fertility studies with palbociclib have not been conducted; however, in repeat-dose toxicity studies, testicular degeneration was observed. [redacted].

The applicant plans to communicate all safety events through labeling, and therefore did not submit a REMS.

4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

- Submission of study report and datasets from the ongoing Study A5481008, PALOMA2, "A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease".
- Submission of a detailed plan to address determination of a prognostic or predictive biomarker in PALOMA2 (A5481008). Specifically, p16 loss ([redacted] and other assays to be specified in the applicant's plan) and retinoblastoma expression should be analyzed in all patients. Additional biomarkers being examined should also be provided in this plan. Submission of a report at the end of the study evaluating the effect of these biomarkers on prognosis and prediction of palbociclib effect.

5 DISCUSSION

Palbociclib is an oral, first in class, cyclin kinase dependent 4/6 inhibitor used in combination with letrozole with the proposed indication for the treatment of ER-positive, HER2 negative advanced breast cancer in postmenopausal women who have not received previous systemic treatment for their advanced disease.

Current FDA-approved therapies for the treatment of ER-positive, HER2-negative advanced breast cancer include endocrine therapies, such as letrozole, anastrozole, exemestane, fulvestrant, and tamoxifen. Nausea was common amongst all these agents. Fatigue was common between exemestane and fulvestrant compared with palbociclib. Serious adverse events seen with these other agents were mainly related to bone effects. Hyperlipidemia was a common effect seen between letrozole and anastrozole. With

tamoxifen, a boxed warning was used to describe effects of pulmonary embolism, increased uterine malignancies, and stroke. None of these agents required a REMS for approval.

Despite the availability of several medications for the treatment of advanced breast cancer, prognosis remains suboptimal in many patients due to development of resistance, with median overall survival rates ranging approximately four years.[4] The current goals of therapy for advanced breast cancer treatment focus on delaying disease progression. Palbociclib in combination with letrozole was shown to be efficacious by meeting its primary endpoint of PFS, resulting in a 10 month prolongation of PFS over standard of care with letrozole alone, and thus has the potential to fill a medical need in this patient population.

The most frequently reported Grade 3 or 4 TEAEs of palbociclib were neutropenia, leukopenia, and anemia. These adverse events were considered self-limiting and reversible. Neutropenia would be communicated in product labeling under Warnings & Precautions.

A REMS is not necessary to ensure the benefits outweigh the risks of palbociclib for the following reasons:

- Palbociclib progression free survival was demonstrated favorably by 10 months in the palbociclib plus letrozole arm,

- neutropenia, infections, pulmonary embolism, and embryo-fetal toxicity will be addressed in the Warnings and Precautions section of the label as reflected in labeling for other drugs used in the treatment for breast cancer that do not require a REMS,

- the target population for palbociclib will be managed by prescribers who are familiar with the disease and adverse events such as myelopsuppression and thromboembolic events seen with this drug and others used for the treatment of advanced breast cancer.

6 CONCLUSION

DRISK and DOP-1 concur that a REMS is not necessary at this time, for the approval of palbociclib, and the management of the risks associated with palbociclib treatment can be managed through professional labeling. Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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